GRAFTS OF TROPHIC FACTOR SECRETING CELLS IN RODENTS AND NONHUMAN PRIMATE MODELS OF NEURODEGENERATIVE DISEASE, J.H. Kordower and D. Emerich, Department of Neurological Sciences and Research Center for Brain Repair, Rush Presbyterian Medical Center, Chicago, IL 60612.

This presentation will describe studies in which grafts of encapsulated cells genetically modified to secrete trophic factors prevent the degeneration of neurons which are selectively vulnerable in neurodegenerative disease. Six Rhesus aged monkeys (between 24 and 29 years old) received fornix transections followed by intraventricular transplants of polymer-encapsulated baby hamster kidney (BHK) fibroblasts which had (n=3) or had not (n=3) been genetically modified to secrete human nerve growth factor (hNGF). Monkeys receiving lesions and control grafts displayed extensive reductions in the number of ChAT (57-75%) and p75 NGFr-immunoreactive (53%) medial septal neurons ipsilateral to the lesion/implant. In contrast, monkeys receiving transplants of encapsulated hNGF-secreting cells display only a modest loss of ChAT-(0-36%) and p75 NGFr(7-22.4%) -immunoreactive septal neurons. All monkeys receiving the hNGF-secreting implants, but none receiving control implants, displayed robust sprouting of cholinergic fibers within the septum ipsilateral to the transplant. Just prior to sacrifice, the capsules were retrieved and determined to contain viable BHK cells releasing biologically relevant levels of hNGF. These data demonstrate that hNGF can provide trophic and tropic influences to aged primate basal forebrain supporting the contention that hNGF may prevent basal forebrain degeneration in Alzheimer's disease.

In the second series of experiments, polymer encapsulated cells genetically modified to secrete human NGF or CNTF were grafted into rodent models of Huntington's disease (HD). Unilateral striatal grafts of hNGF-secreting cells induced hypertrophy and significantly increased the optical density of intact ChAT-ir striatal neurons 1, 2, and 4 weeks post-transplantation relative to rats receiving identical grafts missing only the hNGF construct. NGF secreting grafts also induced hypertrophy of noncholinergic neuropeptide Y-ir striatal neurons. Lastly, a DHFR-based expression vector containing the human ciliary neurotrophic factor (hCNTF) was transfected into baby hamster fibroblast cells (BHK). Using an immunoisolatory polymeric device, encapsulated BHK-control cells and those secreting hCNTF (BHK-hCNTF) were transplanted unilaterally into the rat lateral ventricle. Seven days later, the same animals received unilateral injections of quinolinic acid into the ipsilateral striatum. Nissl stained sections demonstrated that BHK/hCNTF cells attenuated the extent of striatal damage produced by quinolinic acid. BHK-hCNTF grafted animals displayed only a 12% loss of ChAT-ir striatal neurons following intrastriatal quinolinic acid compared to an 81% loss of striatal ChAT-ir neurons seen in BHK-control rats. BHK-hCNTF grafted rats also displayed only a 20% loss of GAD-ir striatal neurons compared to a 72% loss of GAD-ir striatal neurons in BHK-control grafted animals. These results support the concepts that implantation of polymer-encapsulated hCNTF-releasing cells can be used to protect striatal neurons from excitotoxic damage and this strategy may ultimately prove relevant for the treatment of HD.